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REMARKS

Claims 1, 4-11, 46, and 47 are pending in this application. Claims 2 and 3 have been cancelled without prejudice. Claims 12-45 have been withdrawn, due to a Restriction Requirement. Claims 7, 8, and 11 have been amended to better define the invention. New Claims 46 and 47 have been added to recite a preferred embodiment of the Applicants' invention. Support for Claims 46 and 47 can be found in the specification, for example, on page 9, lines 12-16. No new matter has been added. Favorable reconsideration and allowance of the subject application are respectfully requested in view of the following comments.

Claim 7 has been rejected under 35 U.S.C. § 112, first and second paragraphs for being indefinite because of the use of the expression "additional medicaments." It is submitted that the expression "additional medicaments" is clear and well known to those of ordinary skill in the art. Solely to expedite prosecution, however, Claim 7 has been amended by replacing the phrase "medicaments" with the term "steroids." Support is found in the specification at, for example, page 7, line 25 through page 8, line 4. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claims 1 and 4-11 have been rejected under 35 U.S.C. § 112, second paragraph for being indefinite for the use of the phrase "17 β -estradiol-3-lower alkanoate." Without agreeing with the propriety of the Examiner's rejection, Claims 1 and 5 have been amended to recite 17 β -estradiol-3-acetate, a particularly preferred embodiment of the invention. Accordingly, this rejection is rendered moot.

Claims 1-3, 5, 10, and 11 have been rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 3,478,070 (Stein).

Claim 1 recites a pharmaceutical dosage unit for oral administration to a human female. The unit comprises a therapeutically effective amount of 17 β -estradiol-3-acetate and a pharmaceutically acceptable carrier.

Stein relates to a process for preparing polyhydroxy 13-alkylgona-(and 8-isogona)-1,3,5(10)-triene 3-ols and Δ^7 -, $\Delta^{8(9)}$ -, $\Delta^{9(11)}$ - and $\Delta^{8(9), 14(15)}$ - dehydro analogs thereof by selective acylation in the 3-position. This selective acylation involves reaction with alkali metal lower alkoxide in a lower alkanol, displacement of the lower alkanol with a polar inert solvent and acylation in the solvent. The products of Stein are said to be hormonally active, especially estrogenically and anti-lipemically. The products of Stein are also said to be intermediates in preparing hormonally active steroids, such as 17 α -ethinylestradiol (see Col. 1, lines 37-38 and 44-59). Stein teaches (see Col. 1, line 52 and Col. 1, line 70 to Col. 2, line 2) that it is an object of the invention to selectively acylate the 3-position in order to transform other functional groups and to then regenerate the 3-hydroxyl group.

The Office Action suggests Stein for the general teaching of making 3-acylated derivatives of d-estradiol and providing such derivatives in a unit dose form. Example 3 of Stein prepares d-estradiol-3-acetate and Stein mentions its usefulness for the treatment of menopause. (See Col. 6, lines 58-61). The Examiner clearly recognizes that Stein, however, does not disclose a composition comprising a 17 β -estradiol-3-acetate. Claim 1 of the present invention is directed to a composition that contains a 17 β -estradiol-3-acetate.

Even if Stein can properly be deemed to support a prima facie case of obviousness with respect to a pharmaceutical dosage unit for oral administration containing 17 β -estradiol-3-acetate, it is respectfully submitted that any such conclusion is clearly rebutted by the unexpected advantageous properties of the present invention. Most significantly, Applicants have unexpectedly discovered that a 17 β -estradiol-3-acetate has an enhanced bioavailability

compared to 17 β -estradiol. The Examiner is directed to Example 3 of the present specification, which illustrates the enhanced bioavailability of 17 β -estradiol-3-acetate over 17 β -estradiol (see Example 3, Table 1). Based on a preliminary evaluation of the data, the inventors reported that the relative bioavailability of estradiol from 17 β -estradiol-3-acetate was 15% greater than an equivalent amount of micronized 17 β -estradiol, when administered to postmenopausal females. However, upon further evaluation of the data, the relative bioavailability of estradiol in the 17 β -estradiol-3-acetate was determined to be higher than originally reported. This is discussed in the accompanying Declaration submitted by Dr. Tina deVries, who is one of the named inventors. In her Declaration, Dr. deVries confirms that the relative bioavailability of estradiol was found to be 19% greater for 17 β -estradiol-3-acetate over 17 β -estradiol. Thus, the pharmaceutical dosage form of the present invention is clearly and unexpectedly advantageous over the oral administration of a 17 β -estradiol containing pharmaceutical composition. Stein clearly does not recognize the unexpectedly higher relative bioavailability of the 17 β -estradiol-3-acetate when delivered orally in a pharmaceutical composition. Accordingly, it is respectfully submitted that presently amended Claim 1 is patentable over Stein.

Claims 5, 10, and 11 directly depend from Claim 1. For at least the same reasons discussed above in connection with Claim 1, Claims 5, 10, and 11 are patentable over Stein.

In addition, Claims 4 and 6-9 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 3,478,070 (Stein et al.) in view of an article by Remington, "The Science and Practice of Pharmacy," 19th ed., 1995 (pp. 1413, and 1623-1626) (Remington article) and an article by Wolfe et al., "Effects of Continuous Conjugated Estrogen and Micronized Progesterone Therapy Upon Lipoprotein Metabolism in Postmenopausal Women," Journal of Lipid Research, (2000; 41: 368-375) (Wolfe article). Applicants

respectfully submit that neither Remington nor Wolfe, whether taken alone or together, remedy the deficiencies of Stein.

The Examiner is, with respect, indulging in hindsight analysis by stating that it would be obvious to keep the moisture content below 8% and/or to incorporate an inhibitor of hydrolysis. Stein neither discloses nor suggests that 17 β -estradiol-3-acetate is sensitive to hydrolysis. For example, column 6, lines 21-22 teaches that the compounds of Formula I can be formulated in liquid or solid forms – **equal** status is given to these two options. Further on, at column 6, lines 34-45, it is taught that the liquid preparations can be solutions, suspensions or emulsions in a pharmaceutically acceptable carrier such as sterile **water**. An aqueous suspension is specifically taught as being suitable for oral use. Thus, by listing solid and liquid forms as equal alternatives, the problem of achieving a pharmaceutical dosage unit for oral administration comprising a therapeutically effective amount of 17 β -estradiol-3-acetate is not even contemplated by Stein.

The Examiner, by rejecting Claims 4 and 6-9 over Stein and further in view of the Remington article and the Wolfe article, suggests that either Stein and Remington or Stein and Wolfe address the same problem. Absent guidance in Stein to consider hydrolysis as an issue, there is nothing to motivate a person skilled in the art to combine the disclosure of Remington or Wolfe with the disclosure of Stein.

The Examiner states that Remington discloses that “silica gel (colloidal silicon dioxide)” is a pharmaceutical ingredient that is used as a tablet moisture adsorber, a glidant and as a suspending and thickening agent. Applicants respectfully submit that this statement is inaccurate. In particular it should be noted that colloidal silicon dioxide is not silica gel – colloidal silicon dioxide is a silica **powder**, a completely different entity which acts as a glidant in promoting flowability of the granulation. On the other hand, silica gels are amorphous forms

of polysilicic acids and are available in various commercial grades of hydration and porosity. Generally, they find use as gas adsorbents, desiccants, thickeners, and gelling agents.

Applicants respectfully submit that there is simply nothing in either Stein or Remington that would have motivated a person skilled in the art to combine the disclosure of Remington with the disclosure of Stein. Moreover, even if combined, there is clearly no suggestion of including an ester hydrolysis inhibitor in the pharmaceutical composition of 17 β -estradiol-3-acetate or that the moisture of such a composition be maintained below the recited percent of Claim 4. The Examiner's conclusion that one skilled in the art would use colloidal silicon dioxide to reduce the moisture content of a 17 β -estradiol-3-acetate is clearly impermissible hindsight analysis since there is simply no suggestion in Stein to maintain the moisture content of such a pharmaceutical composition below a given level. Accordingly, it is respectfully submitted that Claims 4 and 6 are also clearly patentable.

The Examiner acknowledges that Wolfe is simply cited for the purpose of illustrating that conjugated equine estrogens and micronized progesterone have been previously administered at the same time, whether in the same pharmaceutical dosage unit or in two separate dosage units. Wolfe is entirely silent on the actual pharmaceutical dosage unit(s) being administered. Furthermore, conjugated equine estrogens contain sulfate derivatives, as taught at page 3 of the present description, but do not contain any 17 β -estradiol-3-acetate. Applicants respectfully submit an extract from Martindale, the Thirty Second edition, teaching that conjugated estrogens contain 52.5 to 61.5% sodium estrone sulfate and 22.5 to 30.5% sodium equilin sulfate (equilin is 3-hydroxyestra-1,3,5(10),7-tetraen-17-one) and also contains, as sulfate conjugates, 13.5 to 19.5% 17 α -dihydroequilin, 2.5 to 9.5% 17 α -estradiol and 0.5 to 4.0% 17 β -dihydroequilin. Wolfe does not disclose any pharmaceutical dosage unit of 17 β -estradiol or any

3-acylated derivative thereof. Furthermore, Wolfe clearly does not disclose any pharmaceutical dosage unit of 17 β -estradiol-3-acetate. Thus, Claims 7-9 are clearly patentable.

Wherefore, none of the cited art, whether taken alone or together, discloses or suggests the inclusion of a 17 β -estradiol-3-acetate in a pharmaceutical dosage unit, let alone the enhanced bioavailability of a 17 β -estradiol-3-acetate. Accordingly, Applicants respectfully requests favorable reconsideration and early passage to issue of the present application.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

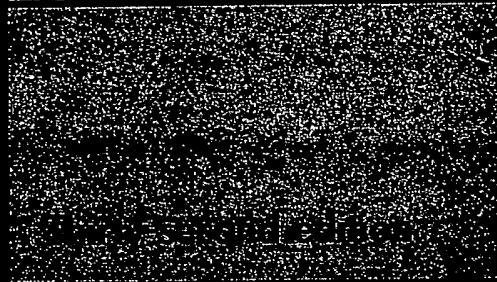
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